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SYNTHESIS AND ANTIMICROBIAL ACTIVITY SCREENING OF NEW CYCLIC IMIDES COMPRISING ANTIPYRINE AND OXAZOLE CYCLES

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ABSTRACT : In this work, a variety of new cyclic imides bearing both antipyrine and oxazole moieties were synthesized. Synthesis of the new imides was based on the key compound [2] 2-amino-4-(antipyrine-4-yl-amino) oxazole, which was prepared via reaction between 4-(2-chloro acetamido) antipyrine [1] and urea. The target imides were synthesized by two steps in the first one compound [2] was introduced in reaction with different cyclic anhydrides affording amic acids [3-6] and these inturn were dehydrated by fusion in the second step affording the target imides [7-10]. Naphthalimide [11] is the only imide that was synthesized by direct fusion of key compound [2] with napthalic anhydride.

Key words : Cyclic imides, antipyrine, oxazole, amic acids, key compound.

INTRODUCTION

Azoles are very important heterocycles that form the basis of different drugs, pharmaceuticals and agrochemical products due to their wide spectrum of biological activities such as antimicrobial, anti-inflammatory, anticancer and antiviral activities (Al-Azzawi and Hamd, 2014; Mahdi and AL-Azzawi, 2013). On the other hand, cyclic imides have been extensively investigated because of the wide range of biological activities (Latief and Al-Azzawi, 2018; Al-Azzawi and Raheem, 2017). They exert, as well as due to their importance as synthetic intermediates. Nowdays, focus has been placed on this important class of compound for their potential new applications especially in the area of pharmaceutical chemistry (Al-Azzawi and Hassan). Keeping in minal all these points, it seems worthwhile to combine these two biologically active components (cyclic imides and azoles) in one molecule, which may exhibit different biological activities (Alaa ***et al***, 2011).

Thus the present work involved synthesis a variety of new cyclic imide containing two azole moieties (antipyrine and oxazole).

The newly synthesized molecules are expected to exhibit biological activity since they are built from three biologically active segments.

MATERIALS AND METHODS

The used chemicals in this work were purchased by Aldrich, BDH, Fluka and Merk companies.

Synthesis of 4-(2-chloro acetamido) antipyrine[1] (Al-Azzawi, 2011)

A mixture of (0.01mol, 2.03g) of 4-aminoantipyrine and (0.01mol, 0.56gm) of chloro acetyl chloride in (25 mL) chloroform was refluxed in the presence of K_2CO_3 (0.01mol, 0.69gm) for about 12hrs. After removing excess solvent the residue was stirred with water (25 mL). The formed precipitate was filtered, washed with sodium bicarbonat solution (5%) and subsequently with distilled water, dried and purified by recrystallization from ethanol to afford Yellow crystals in (84%) Yield and m.p (139-141^{0}C).

Synthesis of 2-amino-4- (antipyrine-4-yl-amino) oxazole [2] (Singh *et al*, 2010)

To a methanolic solution of compound [1] (0.01mol, 2.79gm) in (25 mL) methanol, urea (0.01mol, 0.6gm) was added then the mixture was refluxed for (12 hrs). After distillation of methanol the residue was poured into crushed ice with stirring and the obtained solid was filtered, dried then recrystallized from methanol to affordeda yellow crystals. Yield (93%), m.p (125-126^{0}C).

Synthesis of N-[4-(antipyrine-4-yl- amino) oxazole-2-yl] amic acids [3-6] (Al-Azzawi and Raheem, 2017)

The titled amic acids [3-6] were synthesized via addition of (0.01mol, 2.85gm) of compound [2] dissolved in (30 mL) dry acetone to (0.01mol) of cyclic anhydride (maleic, phthalic, citraconic or tetrachlorophthalic anhydrides) dissolved in (20 mL) dry acetone with cooling and stirring. After completion of addition the mixture was

stirred at room temperature for additional two hours then the obtained solid was filtered, washed with diethyl ether twice, dried then recrystallized from a suitable solvent. Physical properties of amic acids [3-6] are shown in Table 1.

Synthesis of N-[4-(antipyrine-4-yl-amino) oxazole-2-yl] imides [7-10] (Al-Azzawi and Hassan)

The titeld imides [7-10] were synthesized via dehydration of amic acids [3-6]. Amic acid was heated until fusion then temperature was kept at ten degrees above melting point of amic acid for two hours. The resulted product was left at room temperature and the obtained solid was purified by recrystallization from a suitable solvent.

Synthesis of N-[4-(antipyrine-4-yl-amino)oxazole-2-yl] naphthalimide[11] (Al- Azzawi and Faiq, 2017)

The titled imide [11] was synthesized via heating the mixture of (0.01 mol, 2.85gm) of compound [2] with (0.01 mol, 1.98gm) of naphthalic anhydride until complete fusion. The mixture was kept at fusion temperature for two hours, then cooled and the resulted solid was purified by recrystallization. Physcial properties of the prepared imides are shown in Table 2.

Antibacterial activity study

The cup plate method was used in studying the antibacterial activity of the prepared cyclic imides against many types of bacteria using gentamicin as the reference compound. Nutrient agar medium was used beside DMSO as sample solution and sample volume for all the studied compounds was fixed as (0.1 mL). Cups were scooped out of agar medium contained in a petridish, which was previously incubated with the microorganisms. The test compound solution (0.1mL) was added in the cups and the petridishes were incubated at 37^0C for 48 hrs. Zones of inhibition caused by each compound was measured in mm and the results are listed in Table 5.

RESULTS AND DISCUSSION

In continuation of our interest in synthesis of different cyclic imides bearing different heterocycles the present work involved building of new molecules by combination of two azole cycles namely (antipyrine and oxazole) with different imide cycles together in the same molecule. The new target molecules were expected to exhibit high biological activity since they contain three known biologically active components. Synthesis of the target compounds involved many steps, which are summarized in scheme (1).

In the first step 4-amino antipyrine was introduced in nucleophilic substitution reaction with chloro acetyl chloride producing compound [1] 4-(2-chloro acetamido) antipyrine which in turn was introduced in the second step in nucleophilic reaction with urea followed by ring closure producing compound [2] 2-amino-4-(antipyrine-4-yl-amino) oxazole.

By these two steps we build a new molecule that contains two heterocycles antipyrine linked to oxazole ring through (NH) group.

In compound [2] the presence of amino group at position two in oxazole ring gives the opportunity for introducing this compound in reaction with different cyclic anhydrides in the third step producing the corresponding amic acids [3-6]N-[4-(antipyrine-4-yl-amino) oxazole-2-yl] amic acids.

Dehydration of amic acids [3-6] in the fourth step by fusion method afforded the corresponding N-[4-(antipyrine-4-yl-amino) oxazole-2-yl] imides [7-10].

In the case of N-[4-(antipyrine-4-yl-amino) oxazole-2-yl] naphthalimide [11] the synthesis is performed by fusion the mixture of compound [2] with naphthalic anhydride (Al- Azzawi and Faiq, 2017).

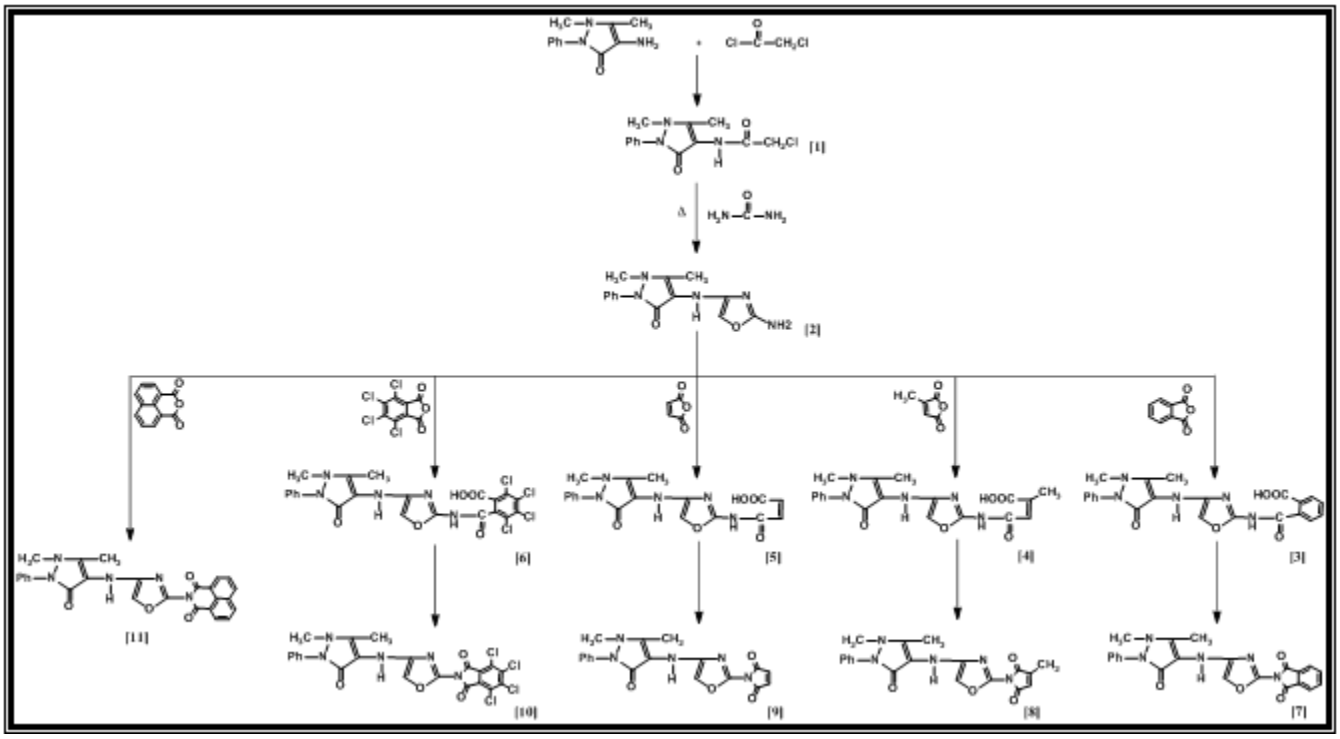
Characterization of the synthesized compounds was performed by depending on FTIR and NMR spectral data.

FTIR spectrum of compound [1] showed absorption band at 3188 cm^{-1} due to υ (N-H) amide and other bands at 3039 cm^{-1}, 2929 cm^{-1} and 2873 cm^{-1}, which are due to υ (C-H) aromatic, asym. and sym. υ(C-H) aliphatic, respectively. The spectrum showed also clear absorption bands at 1691 cm^{-1}, 1639 cm^{-1}, 1614 cm^{-1} and 788 cm^{-1} which are attributed to υ (C=O) amide, υ (C=O) in antipyrine ring, υ (C=C) and υ (C-Cl), respectively (Aruldhas, 2014).

FTIR spectrum of compound [2] showed appearance of two clear absorption bands at (3442) cm^{-1} and (3340) cm^{-1} due to asym. and sym. υ (NH_2) proving the success of compound [2] formation.

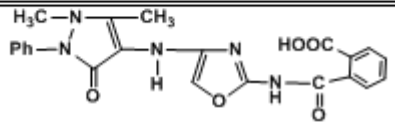
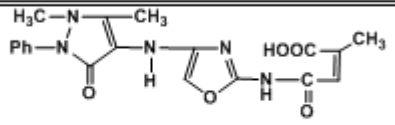
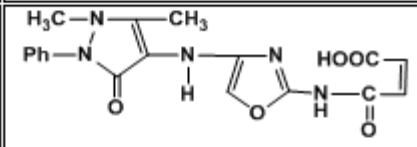
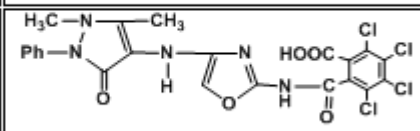
Other bands appeared at 1639, 1614, 1589, 1240 and 1164 cm^{-1}, which are due to ‹ (C=O) antipyrine ring, υ (C=N), υ (C=C), asym. and sym. υ (C-O-C) oxazole, respectively. Besides absorption bands due to υ (C-H) aromatic, asym. and sym. υ (C-H) aliphatic appeared at (3049) cm^{-1}, (2930) cm^{-1} and (2869) cm^{-1}, respectively.

FTIR spectra of amic acids [3-6] showed clear absorption bands at (3434-3458) cm^{-1} and (3182-3423) cm^{-1} due to υ (O-H) and υ (N-H), bands at (1690-1728) cm^{-1} and (1635-1704) cm^{-1} are due to υ (C=O) carboxyl and υ (C=O) amide and bands at (1606-1639) cm^{-1} and (1590-1616) cm^{-1} are due to υ (C=N) and υ (C=C),



Scheme 1 : Target compounds synthesis steps.

Table 1 : Physical properties of amic acids [3-6].

Comp. No.	Compound structure	Colour	Melting Points °C	Yield %	Recrystallization Solvent
3		Yellow	132-133	81	Ethanol
4		Yellow	121-123	78	Acetone
5		Pale Yellow	118-120	93	Acetone
6		Yellow	140-142	86	Ethanol

respectively. Other absorption bands appeared at (3018-3068) cm^{-1}, (2910-2960) cm^{-1}, (2862-2890) cm^{-1}, (1224-1284) cm^{-1} and (1118-1186) cm^{-1} are due to υ (C-H) aromatic, asym. and sym. υ (C-H) aliphatic and asym. and sym. υ (C-O-C) oxazole, respectively.

^{1}H-NMR spectrum of amic acid [4] showed clear signals at (δ = 1.94-2.23) ppm belong to two (CH_3) protons and signals at (δ = 3.12-3.22) ppm belong to (-N-CH_3) protons. Signals belong to (NH) amine proton and vinylic protons appeared at (δ = 4.1) ppm and (δ =

Table 2 : Physical properties of cyclic imides [7-11].

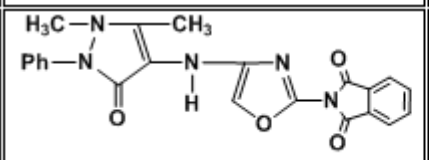
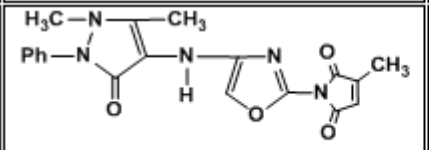
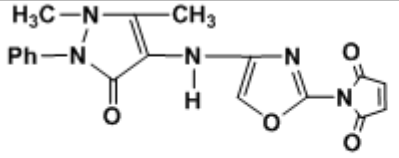
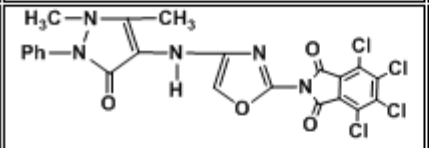
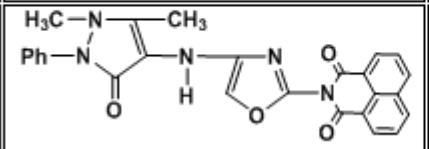
Comp. No.	Compound structure	Color	Melting Points °C	Yield %	Recrystallization Solvent
7		Dark Brown	188-190	79	Acetone
8		pale Brown	175-177	81	Cyclohexane
9		Brown	242-245	90	Cyclohexane
10		Dark Brown	>300	71	Acetone
11		Black	171-174	69	Dioxane

Table 3 : FTIR Spectral data (cm^{-1}) of amic acids [3-6].

Comp. No	υ (O-H)) υ(N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) carboxyl	υ(C=O) Amide	υ (C=N)	υ(C=C)	υ(C-O-C) Oxazole
3	3458 3394 3188	3018	2910 2871	1690	1635	1606	1590	1284 1186
4	3438 3344 3191	3055	2960 2890	1714	1691	1639	1590	1242 1137
5	3446 3423	3068	2950 2883	1718	1689 1637	1622	1591	1224 1137
6	3434 3384 3182	3045	2950 2862	1728	1704 1693	1639	1616	1282 1118

7.28-7.36) ppm, while signals belong to aromatic protons, (NH) amide proton and (OH) carboxyl proton appeared at (δ = 7.47-8.3) ppm, (δ = 9.6) ppm and (δ = 11.2) ppm, respectively.

^{13}C-NMR spectrum of amic acid [4] showed signals at (δ = 10.27-11.59) ppm, (δ = 30.02) ppm and (δ = 35.65-36.3) ppm which are belong to CH_3 carbon, CH_3 (citracon) carbon and (-N-CH_3) carbon, respectively.

Signals belong to aromatic carbons appeared at (δ = 100.12-152.65) ppm, carbons belong to vinylic carbons in imide cycle, antipyrine cycle and oxazole cycle appeared at (δ = 153.33-166.23) ppm and signal belong

Table 4 : FTIR Spectral data (cm^{-1}) of cyclic imides [7-11].

Comp. No	υ (N-H)	υ (C-H) Aromatic	υ (C-H) Aliphatic	υ (C=O) Imide	υ(C=O) Antipyrine	υ (C=N)	υ (C=C)	υ (C-N) Imide	υ (C-O-C)
7	3191	3045	2933 2860	1772 1722	1668	1625	1591	1382	1182
8	3429 3309	3047	2945 2880	1716	1652	1652	1591	1313	1176
9	3427	3056	2927 2880	1718	1652	1652	1595	1400	1184
10	3371 3137	3049	2920 2860	1770 1716	1631	1631	1595	1369	1195 1126
11	3124	3045	2929 2810	1772 1737	1683	1683	1587	1375	1234 1124

Table 5 : Inhibition zones of antimicrobial activity of cyclicimides.

Comp. No	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*E.coli*	*Pseudomonas*	*Candida albicans*
1	++	++	++	++	
2	+++	+++	++	++	
8	+++	+++	+++	+++	
9	++	++	++	++	++
10	+++	+++	++	++	++
11	+++	+++	+++	+++	+++
Gentamicin	+++	+++	+++	+++	+++

Highly active = +++ = inhibition zone > 11 mm, Moderately active = ++ = inhibition zone 8-11mm.

to (C=N) carbon appeared at (δ = 168) ppm. Other signals appeared at (δ = 169.73)ppm, (δ = 170.97) ppm and (δ = 172.15) ppm, which are belong to (C=O) antipyrine, (C=O) amide and (C=O) carboxyl carbons, respectively.

FTIR spectra of the newly synthesized imides [7-11] showed two clear characteristic absorption bands at (1770-1772) cm^{-1} and (1716-1737) cm^{-1} which are due to asym. υ (C=O) imide and sym. υ (C=O) imide, respectively. Other absorptions bands appeared at (3124-3429) cm^{-1}, (3045-3056) cm^{-1}, (2920-2945) cm^{-1} and (2810-2880) cm^{-1} which are due to υ (N-H), υ (C-H) aromatic, asym. and sym. υ (C-H) aliphatic while absorption bands due to υ (C=O) antipyrine, υ (C=N), υ (C=C), υ (C-N) imide, asym. and sym. υ (C-O-C) oxazole appeared at (1631-1683) cm^{-1}, (1625-1683) cm^{-1}, (1587-1595) cm^{-1}, (1313-1400) cm^{-1}, (1195-1234) cm^{-1} and (1124-1184) cm^{-1}, respectively (Sliverstine ***et al***, 2005).

FTIR spectraldata of amic acids [3-6] and imides [7-11] are listed in Tables (3) and (4). ^{1}H-NMR spectrum of imide [7] showed signals at (δ = 2.03-2.24) ppm and (δ = 3.03) ppm, which are belong to (CH_3) protons and (-N-CH_3) protons while signals belong to (NH) proton, vinylic proton and aromatic protons appeared at (δ = 3.51) ppm, (δ = 7.19) ppm and (δ = 7.38-7.97) ppm, respectively.

^{13}C-NMR spectrum of imide [7] showed signals at (δ = 10.65-11.58) ppm and (δ = 35.44-36.48) ppm belong to (CH_3) carbon and (-N-CH_3) carbons. Signals belong to aromatic carbons, vinylic carbons in (imide ring, antipyrine ring and oxazole rings) and (C=N) carbon appeared at (δ = 100.91-152.65) ppm, (δ = 154.5- 161.87) ppm and (δ = 162.14) ppm, while signals belong to (C=O) antipyrine carbon and (C=O) Imide carbons appeared at (δ = 166.04) ppm and (δ = 171.80-172.06) ppm.

^{1}H-NMR spectrum of imide [9] showed signal at (δ = 2.09- 2.13) ppm (δ= 3.01) ppm and (δ= 3.98) ppm which are belong to (CH_3) protons, (-N-CH_3) protons and (NH) proton respectively while signals belong to vinylic protons and aromatic protons appeared at (δ= 7.30-7.32) ppm and (δ= 7.5-7.56) ppm.

^{13}C-NMR spectrum of imide [9] showed signal at (δ= 10.64-11.58) ppm, (δ= 35.44-37.06) ppm and (δ= 100.93-152.68) ppm which belong to (CH_3) carbon, (-N-

CH_3) carbon and aromatic carbons. signals belong to vinylic carbons in (imide, antipyrine, oxazole) rings appeared at (δ= 153.82-162.17) ppm, signal belong to (C=N) carbon at (δ= 170.9-170.94) ppm, signal belong to (C=O) antipyrine carbon appeared at (δ = 171-172) ppm and signal belong to (C=O) imide carbons appeared at (δ = 174.49-176.36) ppm (Aruldhas, 2014).

Antimicrobial activity

Antibacterial activitiesofcompounds4-(2-chloro acetamido) antipyrine [1], 2- amino-4- (antipyrine-4-yl-amino) oxazole [2] and the newly synthesized cyclic imides [8-11] were evaluated against four types of bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Eshreshia coli* and *Pseudomonas*. Also antifungal activity of cyclic imides [9-11] were evaluated against *Candida albicans* fungi. Inhibition Zones resulted from each tested compound are listed in Table 5. The resultes indicated that compounds [2], [8], [10] and [11] showed high activity against *staphylococcus aureus* and *Staphylococcus epidermidis* while compound [11] is highly active against *Eshreshia coli*, *Pseudomonas* and *Candida albicans*. Other compounds showed moderate activity against the tested bacteria and *Candida albicans*.

CONCLUSION

Compounds [2], [8], [10] and [11] were synthesized and showed high activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* while compound [11] is highly active against *Eshreshia coli*, *Pseudomonas* and *Candida albicans*.

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